

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/485, 31/47, 31/50, 31/505	A2	(11) International Publication Number: WO 99/21558 (43) International Publication Date: 6 May 1999 (06.05.99)
(21) International Application Number: PCT/US98/22928 (22) International Filing Date: 28 October 1998 (28.10.98) (30) Priority Data: 08/958,816 28 October 1997 (28.10.97) US 09/181,070 27 October 1998 (27.10.98) US (71) Applicant: VIVUS, INC. [US/US]; 605 East Fairchild Drive, Mountain View, CA 94043 (US). (72) Inventors: DOHERTY, Paul, C., Jr.; 10461 Castine Avenue, Cupertino, CA 95014 (US). PLACE, Virgil, A.; 10 Ala Kahua, P.O. Box 44555, Kawaihae, HI 96743 (US). SMITH, William, L.; 6404 Wood Drive, Oakland, CA 94611 (US). (74) Agent: REED, Dianne, E.; Reed & Associates, 3282 Alpine Road, Portola Valley, CA 94028 (US).		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: LOCAL ADMINISTRATION OF PHOSPHODIESTERASE INHIBITORS FOR THE TREATMENT OF ERECTILE DYS- FUNCTION (57) Abstract A method is provided for treating erectile dysfunction in a mammalian male individual. The method involves the local administration of a phosphodiesterase inhibitor or a pharmaceutically acceptable salt, ester, amide or derivative thereof, within the context of an effective dosing regimen. A preferred mode of administration is transurethral. Pharmaceutical formulations and kits are provided as well.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

LOCAL ADMINISTRATION OF PHOSPHODIESTERASE INHIBITORS FOR THE TREATMENT OF ERECTILE DYSFUNCTION

5

TECHNICAL FIELD

This invention relates generally to methods and pharmaceutical compositions for treating erectile dysfunction; more particularly, the invention relates to local administration of phosphodiesterase inhibitors to treat erectile dysfunction.

10

BACKGROUND ART

Impotence is the consistent inability to achieve or sustain an erection of sufficient rigidity for sexual intercourse. It has recently been estimated that approximately 10 million American men are impotent (R. Shabsigh et al., "Evaluation of Erectile Impotence," *Urology* 32:83-90 (1988); W.L. Furlow, "Prevalence of Impotence in the United States," *Med. Aspects Hum. Sex.* 19:13-6 (1985)). Impotence is recognized to be an age-dependent disorder, with an incidence of 1.9 percent at 40 years of age and 25 percent at 65 years of age (A.C. Kinsey et al., "Age and Sexual Outlet," in *Sexual Behavior in the Human Male*; A.C. Kinsey et al., eds., Philadelphia, PA: W.B. Saunders, 218-262 (1948)). In 1985 in the United States, impotence accounted for more than several hundred thousand outpatient visits to physicians (National Center for Health Statistics, National Hospital Discharge Survey, 1985, Bethesda, MD, Department of Health and Human Services, 1989 DHHS publication no. 87-1751). Depending on the nature and cause of the problem, treatments include psychosexual therapy, hormonal therapy, administration of vasodilators such as nitroglycerin and α -adrenergic blocking agents (" α -blockers"), oral administration of other pharmaceutical agents, vascular surgery, implanted penile prostheses, vacuum constriction devices and external aids such as penile splints to support the penis or penile constricting rings to alter the flow of blood through the penis.

A number of causes of impotence have been identified, including vasculogenic, neurogenic, endocrinologic and psychogenic. Vasculogenic impotence,

which is caused by alterations in the flow of blood to and from the penis, is thought to be the most frequent organic cause of impotence. Common risk factors for vasculogenic impotence include hypertension, diabetes, cigarette smoking, pelvic trauma, and the like. Neurogenic impotence is associated with spinal-cord injury, multiple sclerosis, peripheral neuropathy caused by diabetes or alcoholism and severance of the autonomic nerve supply to the penis consequent to prostate surgery. Erectile dysfunction is also associated with disturbances in endocrine function resulting in low circulating testosterone levels and elevated prolactin levels.

Impotence can also be a side effect of various classes of drugs, in particular, those that interfere with central neuroendocrine control or local neurovascular control of penile smooth muscle. Krane et al., *New England Journal of Medicine* 321:1648 (1989). Penile erection requires (1) dilation of the arteries that regulate blood flow to the lacunae of the corpora cavernosum, (2) relaxation of trabecular smooth muscle, which facilitates engorgement of the penis with blood, and (3) compression of the venules by the expanding trabecular walls to decrease venous outflow.

Trabecular smooth muscle tone is controlled locally by adrenergic (constrictor), cholinergic (dilator) and nonadrenergic, noncholinergic (dilator) innervation, and by endothelium-derived vasoactive substances such as vasoactive intestinal polypeptide (VIP), prostanoids, endothelin and nitric oxide. High sympathetic tone (noradrenergic) is implicated in erectile dysfunction, and, in some patients, the disorder can be successfully treated with noradrenergic receptor antagonists. See, e.g., Krane et al., *supra*.

There is also evidence that dopaminergic mechanisms are involved in erectile function. For example, pharmacologic agents that elevate the level of brain dopamine or stimulate brain dopamine receptors increase sexual activity in animals (see, e.g., Gessa & Tagliamonte, *Life Sciences* 14:425 (1974); Da Prada et al., *Brain Research* 57:383 (1973)).

Administration of L-DOPA, a dopamine precursor, enhances sexual activity in male rats. L-DOPA has been used in the treatment of Parkinsonism and is known to act as an aphrodisiac in some patients (Gessa & Tagliamonte, *supra*; Hyppa et al., *Acta Neurologic Scand.* 46:223 (Supp. 43, 1970)). Specific dopamine agonists have been studied for their effects on erectile function. Apomorphine, (*n*-propyl)norapo-morphine,

bromocryptine, amantidine, fenfluramine, L-DOPA and various other pharmacological activators of central dopaminergic receptors have been found to increase episodes of penile erection in male rats (Benassi-Benelli et al., *Arch. int. Pharmacodyn.* 242:241 (1979); Poggioli et al., *Riv. di Farm. & Terap.* 2:213 (1978); Falaschi et al., *Apomorphine and Other Dopaminomimetics*, 1:117-121 (Gessa & Corsini, Eds., Raven Press, N.Y.)). In addition, U.S. Patent No. 4,521,421 to Foreman relates to the oral or intravenous administration of quinoline compounds to treat sexual dysfunction in mammals.

The currently available dopamine agonists, with few exceptions, have found limited use in the treatment of erectile dysfunction because of their peripheral side effects. These effects include nausea and vomiting, postural hypotension, arrhythmias, tachycardia, dysphoria, psychosis, hallucinations, drowsiness and dyskinesias (See, e.g., Martindale *The Extra Pharmacopoeia*, 31st Ed., pages 1151-1168).

Other pharmaceutical methods for treating erectile dysfunction have also proved to be problematic. For example, with Viagra®, the most recently introduced oral drug therapy, not only have significant side effects been encountered, but interaction with other systemically administered medications has posed enormous risks and numerous fatalities have in fact been reported.

The invention described herein provides a means to avoid the above-mentioned problems encountered with the systemic administration of pharmacologically active agents to treat erectile dysfunction. Specifically, the invention relates to methods and formulations for effectively treating erectile dysfunction by locally administering a selected active agent, wherein the active agent is an inhibitor of a phosphodiesterase.

Phosphodiesterases are a class of intracellular enzymes involved in the metabolism of the second messenger nucleotides, cyclic adenosine monophosphate (cAMP), and cyclic guanosine monophosphate (cGMP) (see, e.g., Doherty, "Oral, Transdermal, and Transurethral Therapies for Erectile Dysfunction" in Male Infertility and Dysfunction, Hellstrom, ed., Chapter 34 (New York, New York: Springer-Verlag/Hellstrom, 1997)). Numerous phosphodiesterase inhibitors have previously been described in the literature for a variety of therapeutic uses, including treatment of obstructive lung disease, allergies, hypertension, angina, congestive heart failure and depression (see, e.g., Goodman and

Gilman's *The Pharmacological Basis of Therapeutic* Ninth Edition, Chapter 34). Oral and parenteral administration of phosphodiesterase inhibitors, as alluded to above, have also been suggested for the treatment of erectile dysfunction (Doherty, *supra*; see also PCT Publication Nos. WO 96/16644, and WO 94/28902). The phosphodiesterases have been
5 classified into seven major families, Types I-VII, based on amino acid or DNA sequences. The members of the family vary in their tissue, cellular and subcellular distribution, as well as their links to cAMP and cGMP pathways. For example, the corpora cavernosa contains: type III phosphodiesterases, which are cAMP-specific cGMP inhibitable; type IV phosphodiesterases, the high affinity, high-specificity cAMP-specific form; and type V
10 phosphodiesterases, one of the cGMP-specific forms.

Various compounds are known as inhibitors of phosphodiesterases are known, including vinpocetine, milrinone, amrinone, pimobendan, cilostamide, enoximone, peroximone, vesnarinone, rolipram, RO20-1724, zaprinast, dipyridamole, pentoxifylline, sildenafil citrate (Viagra®), doxazosin, papaverine, prazosin, terazosin, trimazosin, and
15 hydralazine. PCT Publication No. WO 94/28902 discloses a series of pyrazole [4,3-d]pyrimidin-7-ones cGMP phosphodiesterase inhibitors. PCT Publication No. WO 96/16644 also discloses a variety of cGMP phosphodiesterase inhibitors, including griseolic acid derivatives, 2-phenylpurinone derivatives, phenylpyridone derivatives, fused and condensed pyrimidines, a pyrimidopyrimidine derivative, a purine compound, a quinazoline
20 compound, a phenylpyrimidone derivative, an imidazoquinoxalinone derivative or aza analogues thereof, a phenylpyridone derivative, and others.

The following documents are of interest insofar as they relate to the treatment of erectile dysfunction by delivering pharmacologically active agents locally to the penis:

25 U.S. Patent No. 4,127,118 to Latorre describes the injection of vasodilator drugs into the corpora cavernosa of the penis to dilate the arteries that supply blood to the erectile tissues, thereby inducing an erection;

U.S. Patent No. 5,439,938 to Snyder et al. describes the administration of nitric oxide (NO) synthase inhibitors by direct injection of a drug into the corpora

cavernosa, by topical drug administration or transurethral drug administration, for inhibiting penile erection due to priapism and for treating urinary incontinence;

Virag et al., *Angiology-Journal of Vascular Diseases* (February 1984), pp. 79-87, Brindley, *Brit. J. Psychiat.* 143:332-337 (1983) and Stief et al., *Urology* XXXI:483-485 (1988) respectively describe the intracavernosal injection of papaverine (a smooth muscle relaxant), phenoxybenzamine or phentolamine (α -receptor blockers) and a phentolamine-papaverine mixture to treat erectile dysfunction; and

PCT Publication No. WO 91/16021, U.S. Patent No. 4,801,587 to Voss et al., and U.S. Patent Nos. 5,242,391, 5,474,535, 5,686,093 and 5,773,020 to Place et al. relate to the treatment of erectile dysfunction by delivery of a vasoactive agent into the male urethra.

The invention, as noted above, is directed to local administration of pharmacologically active agents to treat erectile dysfunction. The agents are preferably, although not necessarily, Type V phosphodiesterase inhibitors. Surprisingly, it has now been found by the inventors herein that local administration of these phosphodiesterase inhibitors as disclosed herein is highly effective in treating erectile dysfunction, particularly vasculogenic impotence. Local administration of phosphodiesterase inhibitors, and transurethral drug administration in particular, generally enables use of a lower drug dosage, avoids many of the side effects encountered with other modes of administration, and avoids interaction with other systemically administered medications an individual may be taking. The local administration of phosphodiesterase inhibitors, particularly Type V phosphodiesterase inhibitors, to treat erectile dysfunction, accordingly represents an important advance in the treatment of impotence and other erectile disorders.

25

DISCLOSURE OF INVENTION

It is a primary object of the invention to address the above-described need in the art by providing a novel method for treating erectile dysfunction by locally administering an effective amount of a selected phosphodiesterase inhibitor to an individual in need of such therapy.

- 6 -

It is another object of the invention to provide such a method wherein the phosphodiesterase inhibitor is administered transurethrally.

It is still another object of the invention to provide such a method wherein the phosphodiesterase inhibitor is administered via intracavernosal injection.

5 It is yet another object of the invention to provide such a method wherein the phosphodiesterase inhibitor is administered topically.

It is a further object of the invention to provide such a method wherein the phosphodiesterase inhibitor is administered transdermally.

10 It is yet a further object of the invention to provide pharmaceutical formulations for carrying out the aforementioned methods.

It is an additional object of the invention to provide a kit capable of use by an individual for self-administration of a phosphodiesterase inhibitor as provided herein.

15 Additional objects, advantages and novel features of the invention will be set forth in part in the description that follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

In a first aspect of the invention, a method is provided for treating an individual prone to erectile dysfunction, particularly vasculogenic erectile dysfunction, the method comprising locally administering to the individual a pharmaceutical formulation containing a phosphodiesterase inhibitor. Administration of the pharmaceutical formulation is carried out within the context of a predetermined dosing regimen such that the agent is effective in the treatment of erectile dysfunction. The method is especially useful in the treatment of vasculogenic impotence, although other types of erectile dysfunction may also be treated using the present formulations. Drug delivery is preferably effected transurethrally, but the drug may also be administered via intracavernosal injection or using topical or transdermal administration.

20
25

In another aspect of the invention, a pharmaceutical formulation is provided for carrying out the present method for treating erectile dysfunction. The pharmaceutical formulation comprises an effective amount of a phosphodiesterase inhibitor, a carrier or vehicle preferably suitable for the selected mode of administration, and, optionally, a permeation enhancer. The formulation may contain one or more additional active agents,

30

e.g., dopaminergic drugs, smooth muscle relaxants, vasoactive drugs, and additives, e.g., excipients, surfactants, preservatives (e.g., antioxidants), stabilizers, chelating agents, enzyme inhibitors, antibacterial agents and the like, as will be appreciated by those skilled in the art of drug formulation preparation and delivery.

5 In another aspect, a kit is provided to assist an individual in drug administration to carry out the method of the invention. Generally, the kit will include the following components: a pharmaceutical formulation comprising the phosphodiesterase inhibitor to be administered; a device for effecting delivery of the pharmaceutical formulation; a container housing the pharmaceutical formulation during storage and prior to
10 use; and instructions for carrying out drug administration in a manner effective to treat erectile dysfunction.

BRIEF DESCRIPTION OF THE DRAWING

 Figure 1 is an exploded view of one embodiment of a transurethral
15 therapeutic device which may be used in conjunction with the present method.

MODES FOR CARRYING OUT THE INVENTION

Definitions:

20 Before describing the present invention in detail, it is to be understood that this invention is not limited to particular drugs or drug delivery systems, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

 It must be noted that, as used in this specification and the appended claims,
25 the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a phosphodiesterase inhibitor" includes a mixture of two or more such compounds, reference to "a permeation enhancer" includes mixtures of two or more enhancers, and the like.

 In describing and claiming the present invention, the following terminology
30 will be used in accordance with the definitions set out below.

The term "erectile dysfunction" is intended to include any and all types of erectile dysfunction, including: vasculogenic, neurogenic, endocrinologic and psychogenic impotence ("impotence" is used here in its broadest sense to indicate an inability a periodic or consistent inability to achieve or sustain an erection of sufficient rigidity for sexual intercourse; *see* U.S. Patent No. 5,242,391 to Place et al., cited *supra*); Peyronie's syndrome; priapism; premature ejaculation; and any other condition, disease or disorder, regardless of cause or origin, which interferes with at least one of the three phases of human sexual response, i.e., desire, excitement and orgasm (*see* Kaplan, *Disorders of Sexual Desire* (New York, New York: Brunner Mazel Book Inc., 1979)).

10 The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediation of damage. The present method of "treating" erectile dysfunction, as the term is used herein, thus encompasses both prevention of the disorder in a predisposed individual and treatment of the disorder in a clinically symptomatic individual.

15 The term "phosphodiesterase inhibitor" as used herein is intended to mean an agent that is capable of inhibiting or selectively reducing the activity of any one or more phosphodiesterases.

20 The terms "active agent," "drug" and "pharmacologically active agent" are used interchangeably herein to refer to a chemical material or compound that induces a desired effect. In the preferred embodiment herein, the terms refer to a phosphodiesterase inhibitor which is capable of being delivered locally, preferably transurethraly. Included are derivatives and analogs of those compounds or classes of compounds specifically mentioned which also induce the desired effect.

25 The terms "transurethral," "intraurethral" and "urethral" to specify the preferred mode of administration herein are used interchangeably to refer to the delivery of the drug into the urethra such that drug contacts and passes through the wall of the urethra. As noted elsewhere herein, the present method preferably involves delivery of the drug at least about 3 cm and preferably at least about 7 cm into the urethra.

The term "intracavernosal" as used herein refers to an alternative mode of drug administration and involves injection into one or both corpora of the corpora cavernosal tissues of the penis.

5 The term "transdermal" delivery, applicants intend to include both transdermal (or "percutaneous") and transmucosal administration, i.e., delivery by passage of a drug through the skin or mucosal tissue and into the bloodstream. The term "body surface" will sometimes be used herein to refer to either the skin or the mucosal tissue. "Transdermal" delivery is also intended to encompass delivery of a drug by passage across scrotal tissue.

10 The term "topical administration" is used in its conventional sense to mean delivery of a topical drug or pharmacologically active agent to the skin or mucosa.

"Penetration enhancement" or "permeation enhancement" as used herein relates to an increase in the permeability of the urethral wall to the selected pharmacologically active agent, i.e., so that the rate at which the drug permeates through the urethral wall is increased.

15 "Carriers" or "vehicles" as used herein refer to carrier materials suitable for local drug administration. Carriers and vehicles useful herein include any such materials known in the art which is nontoxic and does not interact with other components of the composition in a deleterious manner.

20 By an "effective" amount of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect, i.e., treatment of erectile dysfunction.

Active Agents for Treatment of Erectile Dysfunction:

25 In order to carry out the method of the invention, a selected phosphodiesterase inhibitor is locally administered to an individual prone to erectile dysfunction.

The active agent herein may be any agent which is effective to inhibit the activity of a phosphodiesterase. Suitable phosphodiesterase inhibitors include, but are not limited to, inhibitors of the type III phosphodiesterases (cAMP-specific-cGMP inhibitable

form), the type IV phosphodiesterase (high affinity-high specificity cAMP form) and the type V phosphodiesterases (the cGMP specific form). Additional inhibitors that may be used in conjunction with the present invention are cGMP-specific phosphodiesterase inhibitors other than Type V inhibitors.

5 Examples of type III phosphodiesterase inhibitors that may be administered include, but are not limited to, bypyridines such as milrinone and amirinone, imidazolones such as piroximone and enoximone, dihydropyridazinones such as imazodan, 5-methyl-imazodan, indolidan and ICI118233, quinolinone compounds such as cilostamide, cilostazol and vesnarinone, and other molecules such as bemoradan, anergrelide, siguazodan, 10 trequinsin, pimobendan, SKF-94120, SKF-95654, lixazinone and isomazole.

 Examples of type IV phosphodiesterase inhibitors suitable herein include, but are not limited to, rolipram and rolipram derivatives such as RO20-1724, nitraquazone and nitraquazone derivatives such as CP-77059 and RS-25344-00, xanthine derivatives such as denbufylline and ICI63197, and other compounds such as EMD54622, LAS-31025 and 15 etazolate.

 Examples of type V phosphodiesterase inhibitors include, but are not limited to, zaprinast, MY5445, dipyridamole, and sildenafil. Other type V phosphodiesterase inhibitors are disclosed in PCT Publication Nos. WO 94/28902 and WO 96/16644.

 The compounds described in PCT Publication No. WO 94/28902 are 20 pyrazolopyrimidinones. Examples of the inhibitor compounds include 5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-(5-morpholinoacetyl-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulfonyl)-phenyl]-1-methyl-3-*n*-propyl-1,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-[2-allyloxy-5-(4-methyl-1-piperazinylsulfonyl)-phenyl]-1-methyl-3-*n*-propyl-1,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-[2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulfonyl]-phenyl]-1-methyl-3-*n*-propyl-1,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-[2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulfonyl]phenyl]-1-methyl-3-*n*-propyl-1,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-[5-[4-(2-hydroxyethyl)-1-piperazinylsulfonyl]-2-*n*-propoxyphenyl]-1-methyl-3-*n*-propyl-1,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one, 5- 30 propoxyphenyl]-1-methyl-3-*n*-propyl-1,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-

[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-*n*-propyl-1,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one, and 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-*n*-propyl-1,6-dihydro-7H-pyrazolo[4,3-*d*]pyrimidin-7-one.

The phosphodiesterase inhibitors described in PCT Publication No. WO 96/16644 include griseolic acid derivatives, 2-phenylpurinone derivatives, phenylpyridone derivatives, fused and condensed pyrimidines, pyrimidopyrimidine derivatives, purine compounds, quinazoline compounds, phenylpyrimidinone derivative, imidazoquinoxalinone derivatives or aza analogues thereof, phenylpyridone derivatives, and others. Specific examples of the phosphodiesterase inhibitors disclosed in WO 96/16644 include 1,3-dimethyl-5-benzylpyrazolo[4,3-*d*]pyrimidine-7-one, 2-(2-propoxyphenyl)-6-purinone, 6-(2-propoxyphenyl)-1,2-dihydro-2-oxypyridine-3-carboxamide, 2-(2-propoxyphenyl)-pyrido[2,3-*d*]pyrimidin-4(3H)-one, 7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydro-pyrimido[4,5-*d*]pyrimidine, 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide, 1-ethyl-3-methylimidazo[1,5-*a*]quinoxalin-4(5H)-one, 4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline, 5-ethyl-8-[3-(*N*-cyclohexyl-*N*-methylcarbamoyl)-propyloxy]-4,5-dihydro-4-oxo-pyrido[3,2-*e*]-pyrrolo[1,2-*a*]pyrazine, 5'-methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'-(8'H)-(3'H)-imidazo[2,1-*b*]purin]4'(5'H)-one, 1-[6-chloro-4-(3,4-methylenedioxybenzyl)-aminoquinazolin-2-yl]piperidine-4-carboxylic acid, (6R, 9S)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]-imidazo[2,1-*b*]purin-4-one, 1-*t*-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-*d*]pyrimidin-4-one, 1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-*d*]pyrimidin-4-one, 2-butyl-1-(2-chlorobenzyl)6-ethoxy-carbonylbenzimidazole, and 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline, and 2-phenyl-8-ethoxycycloheptimidazole.

Still other type V phosphodiesterase inhibitors useful in conjunction with the present invention include: IC-351 (ICOS); 4-bromo-5-(pyridylmethylamino)-6-[3-(4-chlorophenyl)propoxy]-3(2H)pyridazinone; 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]-4-piperidine-carboxylic acid, monosodium salt; (+)-cis-5,6a,7,9,9a-hexahydro-2-[4-(trifluoromethyl)-phenylmethyl-5-methyl-cyclopent-4,5]imidazo[2,1-*b*]purin-4(3H)one; furazlocillin; cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-

octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate; 4-bromo-5-(3-pyridylmethylamino)-6-(3-(4-chlorophenyl)propoxy)-3-(2H)pyridazinone; 1-methyl-5-(5-morpholinoacetyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo(4,3-d)pyrimidin-7-one; 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]-4-piperidinecarboxylic acid, monosodium salt; 5 Pharmaprojects No. 4516 (Glaxo Wellcome); Pharmaprojects No. 5051 (Bayer); Pharmaprojects No. 5064 (Kyowa Hakko; see WO 96/26940); Pharmaprojects No. 5069 (Schering Plough); GF-196960 (Glaxo Wellcome); and Sch-51866.

Other phosphodiesterase inhibitors that may be used in the method of this invention include nonspecific phosphodiesterase inhibitors such as theophylline, IBMX, 10 pentoxifylline and papaverine, and direct vasodilators such as hydralazine.

The active agents may be administered, if desired, in the form of salts, esters, amides, prodrugs, derivatives, and the like, provided the salt, ester, amide, prodrug or derivative is suitable pharmacologically, i.e., effective in the present method. Salts, esters, 15 amides, prodrugs and other derivatives of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 4th Ed. (New York: Wiley-Interscience, 1992). For example, acid addition salts are prepared from the free base using conventional methodology, and involves reaction with 20 a suitable acid. Generally, the base form of the drug is dissolved in a polar organic solvent such as methanol or ethanol and the acid is added thereto. The resulting salt either precipitates or may be brought out of solution by addition of a less polar solvent. Suitable acids for preparing acid addition salts include both organic acids, e.g., acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, 25 methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. An acid addition salt may be reconverted to the free base by treatment with a suitable base. Particularly preferred acid addition salts of the 30 active agents herein are halide salts, such as may be prepared using hydrochloric or hydrobromic acids. Conversely, preparation of basic salts of acid moieties which may be

- 13 -

present on a phosphodiesterase inhibitor molecule are prepared in a similar manner using a pharmaceutically acceptable base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, trimethylamine, or the like. Particularly preferred basic salts herein are alkali metal salts, e.g., the sodium salt, and copper salts.

5 Preparation of esters involves functionalization of hydroxyl and/or carboxyl groups which may be present within the molecular structure of the drug. The esters are typically acyl-substituted derivatives of free alcohol groups, i.e., moieties which are derived from carboxylic acids of the formula RCOOH where R is alkyl, and preferably is lower alkyl. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis

10 or hydrolysis procedures. Amides and prodrugs may also be prepared using techniques known to those skilled in the art or described in the pertinent literature. For example, amides may be prepared from esters, using suitable amine reactants, or they may be prepared from an anhydride or an acid chloride by reaction with ammonia or a lower alkyl amine. Prodrugs are typically prepared by covalent attachment of a moiety which results in

15 a compound that is therapeutically inactive until modified by an individual's metabolic system.

Pharmaceutical Formulations and Modes of Administration:

The active agent is administered locally to treat erectile dysfunction, and is

20 accordingly administered in a pharmaceutical formulation suitable for local administration.

Depending on the specific, "local" mode of administration, the pharmaceutical compositions may be in the form of solid, semi-solid or liquid dosage forms, such as, for example, suppositories, powders, liquids, suspensions, creams, ointments, lotions or the like, preferably in unit dosage form suitable for single administration of a

25 precise dosage. The compositions comprise an effective amount of the phosphodiesterase inhibitor in combination with a pharmaceutically acceptable carrier and, in addition, may include other pharmaceutical agents, adjuvants, diluents, buffers, etc.

For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium

30 saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving,

- 14 -

dispersing, etc., an active compound as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, referenced above.

10 The formulation may, for example, be administered transurethraly. For transurethral administration, the formulation comprises a urethral dosage form containing the active agent and one or more selected carriers or excipients, such as water, silicone, waxes, petroleum jelly, polyethylene glycol ("PEG"), propylene glycol ("PG"), liposomes, sugars such as mannitol and lactose, and/or a variety of other materials, with polyethylene glycol and derivatives thereof particularly preferred.

15 Depending on the particular phosphodiesterase inhibitor administered, it may be desirable to incorporate a transurethral permeation enhancer in the urethral dosage form. Examples of suitable transurethral permeation enhancers include dimethylsulfoxide ("DMSO"), dimethyl formamide ("DMF"), N,N-dimethylacetamide ("DMA"),
20 decylmethylsulfoxide ("C₁₀MSO"), polyethylene glycol monolaurate ("PEGML"), glycerol monolaurate, lecithin, the 1-substituted azacycloheptan-2-ones, particularly 1-*n*-dodecylcyclazacycloheptan-2-one (available under the trademark Azone® from Nelson Research & Development Co., Irvine, CA), SEPA® (available from Macrochem Co., Lexington, MA), alcohols (e.g., ethanol), surfactants as discussed above, including, for
25 example, Tergitol®, Nonoxynol-9® and TWEEN-80®, and lower alkanols such as ethanol.

 Transurethral formulations may additionally include one or more enzyme inhibitors effective to inhibit drug-degrading enzymes which may be present in the urethra. Such enzyme inhibiting compounds may be determined by those skilled in the art by reference to the pertinent literature and/or using routine experimental methods. Additional
30 optional components include excipients, preservatives (e.g., antioxidants), chelating agents,

- 15 -

solubilizing agents (e.g., surfactants), and the like, as will be appreciated by those skilled in the art of drug formulation preparation and delivery.

Transurethral drug administration, as explained in U.S. Patent Nos. 5,242,391, 5,474,535, 5,686,093 and 5,773,020 to Place et al., can be carried out in a number of different ways using a variety of urethral dosage forms. For example, the drug can be introduced into the urethra from a flexible tube, squeeze bottle, pump or aerosol spray. The drug may also be contained in coatings, pellets or suppositories which are absorbed, melted or bioeroded in the urethra. In certain embodiments, the drug is included in a coating on the exterior surface of a penile insert. A preferred drug delivery device for administering a drug transurethrally is shown in Figure 1. It is preferred, although not essential, that the drug be delivered at least about 3 cm into the urethra, and preferably at least about 7 cm into the urethra. Generally, delivery at about 3 cm to about 8 cm into the urethra will provide effective results in conjunction with the present method.

Urethral suppository formulations containing PEG or a PEG derivative are particularly preferred urethral dosage forms herein, and may be conveniently formulated using conventional techniques, e.g., compression molding, heat molding or the like, as will be appreciated by those skilled in the art and as described in the pertinent literature and pharmaceutical texts. See, for example, Remington: The Science and Practice of Pharmacy, 19th Ed. (Easton, PA: Mack Publishing Co., 1995), which discloses typical methods of preparing pharmaceutical compositions in the form of urethral suppositories. The PEG or PEG derivative preferably has a molecular weight M_w in the range of about 200 to 2500, more preferably in the range of about 1000 to 2000. Suitable polyethylene glycol derivatives include polyethylene glycol fatty acid esters, for example, polyethylene glycol monostearate, polyethylene glycol sorbitan esters, e.g., polysorbates, and the like. It is also preferred that urethral suppositories contain one or more solubilizing agents effective to increase the solubility of the active agent in the PEG or other transurethral vehicle.

The solubilizing agent may be a nonionic, anionic, cationic or amphoteric surfactant. Nonionic surfactants include: long-chain fatty acids, i.e., acids having the structural formula $\text{CH}_3(\text{CH}_2)_m\text{COOH}$ where m is an integer in the range of 8 to 16; fatty alcohols, that is, alcohols having the structural formula $\text{CH}_3(\text{CH}_2)_m\text{C(H)OH}$, such as lauryl, cetyl and stearyl alcohols; glyceryl esters such as the naturally occurring mono-, di- and

- 16 -

triglycerides; and esters of fatty alcohols or other alcohols such as propylene glycol, polyethylene glycol, sorbitan, sucrose, and cholesterol. Examples of water-soluble nonionic surfactant derivatives include sorbitan fatty acid esters (such as those sold under the tradename Span®), polyoxyethylene sorbitan fatty acid esters (such as those sold under the tradename TWEEN®), polyoxyethylene fatty acid esters (such as those sold under the tradename Myrj®), polyoxyethylene steroidal esters, polyoxypropylene sorbitan fatty acid esters, polyoxypropylene fatty acid esters, polyoxypropylene steroidal esters, polyoxyethylene ethers (such as those sold under the tradename Brij®), polyglycol ethers (such as those sold under the tradename Tergitol®), and the like. Preferred nonionic surfactants for use as the solubilizing agent herein are polyglycol ether, polyoxyethylene sorbitan trioleate, sorbitan monopalmitate, polysorbate 80, polyoxyethylene 4-lauryl ether, propylene glycol, and mixtures thereof. Anionic surfactants which may be used as the solubilizing agent herein include long-chain alkyl sulfonates, carboxylates, and sulfates, as well as alkyl aryl sulfonates, and the like. Preferred anionic surfactants are sodium dodecyl sulfate, dialkyl sodium sulfosuccinate (e.g., sodium bis-(2-ethylhexyl)-sulfosuccinate), sodium 7-ethyl-2-methyl-4-dodecyl sulfate and sodium dodecylbenzene sulfonate. Cationic surfactants which may be used to solubilize the active agent are generally long-chain amine salts or quaternary ammonium salts, e.g., decyltrimethyl-ammonium bromide, dodecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, tetradecyltrimethylammonium chloride, and the like. Amphoteric surfactants are generally, although not necessarily, compounds which include a carboxylate or phosphate group as the anion and an amino or quaternary ammonium moiety as the cation. These include, for example, various polypeptides, proteins, alkyl betaines, and natural phospholipids such as lecithins and cephalins. Other suitable solubilizing agents (e.g., glycerin) may also be used, as will be appreciated by those skilled in the art. The solubilizing agent will be present in the range of approximately 0.01 wt.% to 40 wt.%, more preferably in the range of approximately 5.0 wt.% to 40 wt.%, and most preferably in the range of approximately 10.0 wt.% to 40 wt.%.

It may be desirable to deliver the active agent in a urethral dosage form which provides for controlled or sustained release of the agent. In such a case, the dosage form typically comprises a biocompatible, biodegradable material, typically a biodegradable

- 17 -

polymer. Examples of such polymers include polyester, polyalkylcyanoacrylate, polyorthoester, polyanhydride, albumin, gelatin and starch. As explained, for example, in PCT Publication No. WO96/40054, these and other polymers can be used to provide biodegradable microparticles which enable controlled and sustained drug release, in turn minimizing the required dosing frequency.

The urethral dosage form will preferably comprise a suppository that is on the order of 2 to 20 mm, preferably 5 to 10 mm, in length and less than about 5 mm, preferably less than about 2 mm in width. The weight of the suppository will typically be in the range of approximately 1 mg to 100 mg, preferably in the range of approximately 1 mg to 50 mg. However, it will be appreciated by those skilled in the art that the size of the suppository can and will vary, depending on the potency of the drug, the nature of the formulation, and other factors.

In Figure 1, a suitable transurethral drug delivery device is shown generally at 10. The device comprises a transurethral inserter 11 having an easily graspable segment 12 that has opposing symmetrically concave surfaces 13 and 14 adapted to be held by two fingers. Drug is contained within a urethral suppository (not shown) within shaft 15, which is sized to fit within the urethra. A longitudinal plunger, the tip of which is seen at 16, is slidably insertable into the longitudinal bore contained within shaft 15. To extrude drug into the urethra, shaft 15 is inserted into the urethra, and plunger tip 16 is pushed into segment 12. The inserter 11 is then removed. Prior to use, and during storage, the device is capped with elongate cap 17 which fits snugly over flange 18 at the proximal end of shaft 15. The cap 17 is provided with a series of parallel ridges 19 to facilitate gripping of the cap and removal from inserter 11.

Although the transurethral drug delivery device shown in Figure 1 represents a preferred device for use herein, again, it should be emphasized that a wide variety of device configurations and urethral dosage forms can be used. Examples of other devices suited to deliver a drug transurethrally are those described and illustrated in PCT Publication No. WO 91/16021 and in U.S. Patent Nos. 5,242,391, 5,474,535, 5,686,093 and 5,773,020 to Place et al.

The devices can either be manufactured under sterile conditions, thereby eliminating the need for post-manufacturing sterilization, or they can be manufactured under

- 18 -

non-sterile conditions and then subsequently sterilized by any suitable technique, e.g., radiation sterilization. The devices can be manufactured by typical plastic forming and coating processes known in the art, including molding extrusion, heat forming, dip coating, and the like.

5 Transurethral drug delivery may involve an "active" delivery mechanism such as iontophoresis, electroporation or phonophoresis. Devices and methods for delivering drugs in this way are well known in the art. Iontophoretically assisted drug delivery is, for example, described in PCT Publication No. WO96/40054, cited above. Briefly, the active agent is driven through the urethral wall by means of an electric current
10 passed from an external electrode to a second electrode contained within or affixed to a urethral probe.

Other modes of "local" drug administration can also be employed. For example, the selected active agent may be administered by way of intracavernosal injection, or it may be administered topically, in an ointment, gel or the like, or transdermally,
15 including transscrotally, using a conventional transdermal drug delivery system.

Intracavernosal injection can be carried out by use of a syringe any other suitable device. An example of a hypodermic syringe useful herein, that can be used for simultaneous injection into both corpora, is described in U.S. Patent No. 4,127,118 to Latorre. The injection is made on the dorsum of the penis by placement of the needle to the
20 side of each dorsal vein and inserting it deep into the corpora.

For intracavernosal injection, the active agent to be administered is incorporated into a sterile liquid preparation, typically a solution or suspension in an aqueous or oleaginous medium. This solution or suspension may be formulated according to techniques known in the art using suitable carriers, dispersants, wetting agents, diluents,
25 suspending agents or the like. Among the acceptable vehicles and solvents that may be employed are water, isotonic saline, vegetable oil, fatty esters and polyols.

The phosphodiesterase inhibitors useful herein may also be delivered through the skin using conventional transdermal drug delivery systems, i.e., transdermal "patches" wherein the agent is typically contained within a laminated structure that serves as a drug
30 delivery device to be affixed to the skin. In such a structure, the drug composition is typically contained in a layer, or "reservoir," underlying an upper backing layer. The

laminated device may contain a single reservoir, or it may contain multiple reservoirs. In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Examples of suitable skin contact adhesive materials include, but are not limited to, polyethylenes, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, and the like. Alternatively, the drug-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form. The backing layer in these laminates, which serves as the upper surface of the device, functions as the primary structural element of the laminated structure and provides the device with much of its flexibility. The material selected for the backing layer should be substantially impermeable to the active agent and any other materials that are present.

Preferred formulations for topical drug delivery herein are ointments and creams. Ointments are semisolid preparations which are typically based on petrolatum or other petroleum derivatives. Creams containing the selected active agent, are, as known in the art, viscous liquid or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. The specific ointment or cream base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and nonsensitizing.

Additional pharmacologically active agents may be delivered along with the primary active agent, i.e., the phosphodiesterase inhibitor. Vasoactive agents, particularly vasodilators, are preferred additional agents. Suitable vasoactive agents include, but are not limited to: nitrates and like compounds such as nitroglycerin, isosorbide dinitrate, erythrityl tetranitrate, amyl nitrate, sodium nitroprusside, molsidomine, linsidomine chlorhydrate

- 20 -

("SIN-1"), S-nitroso-N-acetyl-d,l-penicillamine ("SNAP"), S-nitroso-N-cysteine, S-nitroso-N-glutathione ("SNO-GLU") and diazenium diolates ("NONOates"); long and short acting α -blockers such as phenoxybenzamine, dibenamine, doxazosin, terazosin, phentolamine, tolazoline, prazosin, trimazosin, alfuzosin, tamsulosin and indoramin; ergot alkaloids such as ergotamine and ergotamine analogs, e.g., acetergamine, brazergoline, bromerguride, 5 cianergoline, delorgotril, disulergine, ergonovine maleate, ergotamine tartrate, etisulergine, lergotril, lysergide, mesulergine, metergoline, metergotamine, nicergoline, pergolide, propisergide, proterguride and terguride; antihypertensive agents such as diazoxide, hydralazine and minoxidil; vasodilators such as nimodipine, pinacidil, cyclandelate and 10 isoxsuprine; chlorpromazine; haloperidol; yohimbine; Rec15/2739; trazodone; naturally occurring prostaglandins such as PGE₀, PGE₁, PGA₁, PGB₁, PGF_{1 α} , 19-hydroxy-PGA₁, 19-hydroxy-PGB₁, PGE₂, PGA₂, PGB₂, 19-hydroxy-PGA₂, 19-hydroxy-PGB₂, PGE₃, PGF_{3 α} ; semisynthetic or synthetic derivatives of natural prostaglandins, including carboprost tromethamine, dinoprost tromethamine, dinoprostone, lipoprost, gemeprost, 15 metenoprost, sulprostone and tiaprostone; and vasoactive intestinal peptides. Prazosin, prostaglandin E₀, prostaglandin E₁ and prostaglandin E₂ are particularly preferred vasoactive agents to be co-administered with the active agent.

The amount of active agent administered, and the dosing regimen used, will, of course, be dependent on the particular drug selected, the age and general condition of the 20 subject being treated, the severity of the subject's condition, and the judgment of the prescribing physician. Generally, the daily dosage when administered locally will be less than the dosage normally given in conjunction with systemic modes of administration, and typically, the drug will be administered one to four times daily or, with some active agents, just prior to intercourse. Alternatively, a large initial loading dose can be used to achieve 25 effective levels of the agent and can be followed by smaller doses to maintain those levels. A typical daily dose of an active agent as administered locally is generally in the range of approximately 0.1 to 500 mg. Depending on the half-life of the drug and the availability via the chosen route of administration, the dosing regimen can be modulated in order to achieve satisfactory control of the onset of ejaculation. By administering the drug locally, the side 30 effects, drug interactions and disease considerations of systemic (e.g., oral) drug administration are avoided, as is the stigma associated with psychotherapeutic drug therapy.

Kits:

The invention also encompasses a kit for patients to carry out the present method of treating premature ejaculation using local drug therapy. The kit contains the pharmaceutical formulation to be administered, a device for administering the formulation (e.g., a transurethral drug delivery device such as shown in Figure 1), a container, preferably sealed, for housing the drug and device during storage and prior to use, and instructions for carrying out drug administration in an effective manner. The formulation may consist of the drug in unit dosage form. The kit may contain multiple formulations of different dosages of the same agent. The kit may also contain multiple formulations of different active agents.

10 The instructions may be in written or pictograph form, or can be on recorded media including audio tape, video tape, or the like.

Use in Conjunction with Venous Flow Control ("VFC") Device:

In an alternative embodiment of the invention, a pharmaceutical formulation containing the selected phosphodiesterase inhibitor is administered in combination with a venous flow control device such as that described in PCT Publication No. WO 97/47260, entitled "Venous Flow Control Element for Maintaining Penile Erection." Preferred devices are formed from a length of flexible tubing having an integral fastening means, so as to provide for readily adjustable venous flow control when applied to the penis. The device is applied to the base of the penis prior to and during sexual intercourse, such that it effectively enhances retention of blood within the penis without substantially obstructing arterial inflow or becoming too constrictive during the erectile process. Use of the VFC device also enables enhanced effectiveness of local drug therapy, in that the active agent is retained within the penis, allowing movement into the corpus cavernosa. This produces smooth muscle response and a consistent erectile response. In this embodiment, a kit will include the venous flow control device in addition to the components noted above, along with instructions for using the device.

30 It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description

as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

5

EXAMPLE 1

Preparation of urethral dosage form: A transurethral pharmaceutical formulation containing zaprinast, a type V phosphodiesterase inhibitor, is prepared by mixing 0.2 to 1.5 g of zaprinast with a suitable amount of polyethylene glycol, typically 1-5
10 g, molecular weight (M_w) approximately 2000, and heating the mixture to a temperature just high enough to produce a drug-polymer melt. The mixture can then be poured into a mold suitable to provide a suppository, and allowed to cool. The suppository so provided is a unit dosage form suitable for transurethral administration. This procedure can be used with various phosphodiesterase inhibitors, PEGs, and additional components, e.g., enhancers or
15 the like.

The aforementioned method may also be used to prepare urethral suppositories containing other phosphodiesterase inhibitors as the active agent.

EXAMPLE 2

20 A penile insert coated with zaprinast is prepared as follows. An ethylene vinyl acetate rod is formed into an insert having a shaft approximately 10 cm long with a spherical, blunted tip. A dipping bath comprising a 50-50 weight blend of PEG 1450 and PEG 4000 and sufficient zaprinast to attain the desired concentration in the coating is prepared and heated to 70°C. The insert is suspended by its head, dipped into the dipping
25 bath and removed. A penile insert suitable for transurethral administration is thus provided.

The aforementioned procedure may be used to prepare penile inserts coated with any number of other phosphodiesterase inhibitors as well.

- 23 -

EXAMPLE 3

An effective phosphodiesterase-inhibiting dose may be determined using the following procedures.

Transurethral administration: Patients with penile vascular insufficiency are given a single dose of 0.5 g of a phosphodiesterase inhibitor (e.g., zaprinast) transurethrally in a PEG-based urethral suppository. Prior to and approximately 3 hours after administering the inhibitor, blood samples are taken and assayed for plasma phosphodiesterase activity using, for example, high-performance liquid chromatography with fluorimetric detection as described by Lee et al, *J. Chromatography* 421:237-244 (1987). This procedure is repeated at 24 hour intervals with dosage adjusted as necessary.

EXAMPLE 4

The pharmaceutical preparations of Examples 1 and 2 can be used to treat erectile dysfunction in individuals in which the dysfunction is associated, for example, vascular insufficiency. Dosage may be adjusted using the methodology of Example 3. In all instances the individuals are expected to respond positively, although variations in the intensity and duration of erection may be observed depending on dose, formulation and environment. Generally, between approximately 20 and 90 minutes following drug administration, it is expected that an erection may be achieved.

20

EXAMPLE 5

In this experiment, zaprinast, a Type V phosphodiesterase inhibitor, was evaluated for its capability to induce erections in the anesthetized male cat. Adult male cats (3.5 to 5.0 kg) were initially sedated with ketamine and then anesthetized and maintained with supplemental doses of pentobarbital administered through a polyethylene catheter inserted into the left external jugular vein. After exposure of the pubic area, a 25-gauge needle was placed into the left corpus cavernosum for measurement of intracavernous pressure. Vehicle and various doses of zaprinast (5, 10, 50, 100 and 200 µg) were administered by direct injection into the right corpus cavernosum using a 30-gauge needle. All injections were made using a total volume of 200 µl. At the end of the experiment, each

30

- 24 -

animal received a control drug solution containing 1.65 mg papaverine, 25 μ g phentolamine, and 0.5 μ g of prostaglandin E₁ to establish maximal response in each subject. Zaprinast caused dose-related increases in intracavernosal pressure and penile length. Maximal effects were observed at the 100 μ g dose at which intracorporal pressure (70.5 mm of Hg) and penile length (25.75 mm) were 80.5% and 97.5% of the responses seen after injection of the control drug solution (87.6 mm of Hg and 26.40 mm, respectively). These results suggest that a selective Type V phosphodiesterase inhibitor, when administered locally, can induce significant increases in erectile response in a mammalian male. The same or greater effects are expected upon administration of a urethral suppository.

10 Substantially the same results are expected with other Type V phosphodiesterase inhibitors, and with Type III and Type IV phosphodiesterase inhibitors as well.

- 25 -

CLAIMS

1. A method for treating erectile dysfunction in a male individual, comprising locally administering to the individual an effective amount of a phosphodiesterase inhibitor or a pharmaceutically acceptable salt, ester, amide or prodrug thereof, wherein the phosphodiesterase inhibitor is selected from the group consisting of Type IV phosphodiesterase inhibitors, Type V phosphodiesterase inhibitors, and combinations thereof.
2. The method of claim 1 wherein the phosphodiesterase inhibitor is a Type IV phosphodiesterase inhibitor.
3. The method of claim 2, wherein the Type IV phosphodiesterase inhibitor is selected from the group consisting of: rolipram; nitraquazone; xanthines; EMD54622; LAS-31025; etazolate; salts, esters, and analogs thereof; and combinations of any of the foregoing.
4. The method of claim 3, wherein the Type IV phosphodiesterase inhibitor is selected from the group consisting of rolipram, nitraquazone, denbufylline and etazolate.
5. The method of claim 1, wherein the phosphodiesterase inhibitor is a Type V phosphodiesterase inhibitor.
6. The method of claim 5, wherein the Type V phosphodiesterase inhibitor is selected from the group consisting of zaprinast; dipyridamole; pyrazolopyrimidinones; griseolic acid derivatives; 2-phenylpurinones; phenylpyridone derivatives; pyrimidines; pyrimidopyrimidines; purines; quinazolines; phenylpyrimidinones; imidazoquinoxalinones or aza analogues thereof; phenylpyridones; 4-bromo-5-(pyridylmethylamino)-6-[3-(4-chlorophenyl)propoxy]-3(2H)pyridazinone; 1-[4-[(1,3-benzodioxol-5-ylmethyl)amiono]-6-chloro-2-quinazolinyl]-4-piperidine-carboxylic acid, monosodium salt; (+)-cis-5,6a,7,9,9a-hexahydro-2-[4-(trifluoromethyl)-phenylmethyl-5-methyl-cyclopent-

- 26 -

4,5]imidazo[2,1-b]purin-4(3H)one; furazlocillin; cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate; 4-bromo-5-(3-pyridylmethylamino)-6-(3-(4-chlorophenyl)propoxy)-3-(2H)pyridazinone; 1-methyl-5-(5-morpholinoacetyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo(4,3-d)pyrimidin-7-one; and 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]-4-piperidinecarboxylic acid, monosodium salt.

7. The method of claim 6, wherein the Type V phosphodiesterase inhibitor is zaprinast.

10

8. The method of claim 6, wherein the Type V phosphodiesterase is a pyrazolopyrimidinone.

9. The method of claim 8, wherein the Type V phosphodiesterase is sildenafil or a pharmaceutically acceptable salt thereof.

15

10. The method of claim 1, wherein administration is effected transurethrally.

11. The method of claim 1, wherein administration is effected via intracavernosal injection.

20

12. The method of claim 1, wherein administration is effected topically.

13. The method of claim 1, wherein the individual is given a daily dose of phosphodiesterase inhibitor in the range of approximately 0.2 to 1.5 g/day.

25

14. The method of claim 1, wherein the phosphodiesterase inhibitor is administered one to four times in a twenty-four hour period.

30

- 27 -

15. The method of claim 1, wherein the phosphodiesterase inhibitor is contained within a unit dosage pharmaceutical formulation.

5 16. The method of claim 10, wherein the pharmaceutical formulation comprises a urethral suppository containing a pharmaceutically acceptable carrier selected from the group consisting of polyethylene glycol and derivatives thereof.

10 17. A method for treating erectile dysfunction in a male individual, comprising transurethral administration to the individual an effective amount of a Type III phosphodiesterase inhibitor or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

15 18. A pharmaceutical formulation for treating erectile dysfunction in an individual, comprising a urethral dosage form of a phosphodiesterase inhibitor, a carrier suitable for transurethral drug administration, and, optionally, a transurethral permeation enhancer.

20 19. The formulation of claim 18, wherein the phosphodiesterase inhibitor is selected from the group consisting of Type III, Type IV, and Type V phosphodiesterase inhibitors.

20. The formulation of claim 19, wherein the urethral dosage form comprises a suppository.

25 21. The formulation of claim 19, wherein the urethral dosage form comprises a sterile liquid composition containing a phosphodiesterase inhibitor and a carrier suitable for intracavernosal injection.

30 22. The formulation of claim 19, wherein the urethral dosage form comprises a topical formulation.

- 28 -

23. The formulation of claim 22, wherein the topical formulation is an ointment, cream, gel or lotion.

24. A kit for treating erectile dysfunction in an individual, comprising: a
5 pharmaceutical formulation containing a phosphodiesterase inhibitor; a means for
administering the agent; a container for housing the formulation and drug delivery means;
and instructions for using the drug delivery means to administer the drug within the context
of a dosing regimen effective to treat erectile dysfunction.

10

15

20

25

30

1/1

